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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,703	02/09/2001	Rudolf Lucas	2551-55	6732

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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	15

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/779,703	LUCAS ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10 and 19-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10 and 19-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1, 10 and 19-28 are pending in the instant application. Claims 19 and 20 have been amended, claims 2-9 and 11-18 have been canceled and claims 21-28 have been added as requested by Applicant in Paper Number 14, filed March 5, 2003.

Election/Restrictions

2. Applicant's election with traverse of Group II in Paper No. 14 is acknowledged. The traversal is on the ground(s) that search of all the claimed subject matter is not believed to present an undue burden. This is found persuasive and Group I will be rejoined to Group II.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 10 and 19-28 are currently under examination.

Specification

3. The disclosure is objected to because of the following informalities:

3.1 Applicants' amendment to the specification filed Sept. 25, 2002, Paper 7 (Amendment A), was not made according to 37 CFR 1.121. Whole pages cannot be substituted; replacement can only be made by paragraph, replacement section or substitute specification. In addition, a clean copy had not been supplied, and the marked up copy was incorrect (circled in red). See M.P.E.P. 714 Amendments, Applicant's Action:

37 CFR 1.121. Manner of making amendments in application.

(a) Amendments in applications, other than reissue applications. Amendments in applications, other than reissue applications, are made by filing a paper, in compliance with § 1.52, directing that specified amendments be made.

(b) Specification other than the claims and listings provided for elsewhere (§ § 1.96 and 1.825) . —

(1) Amendment by instruction to delete, replace, or add a paragraph. Amendments to the specification, other than the claims and listings provided for elsewhere (§ § 1.96 and 1.825), may be made by submitting:

(i) An instruction, which unambiguously identifies the location, to delete one or more paragraphs of the specification, replace a deleted paragraph with one or more replacement paragraphs, or add one or more paragraphs;

(ii) Any replacement or added paragraph(s) in clean form, that is, without markings to indicate the changes that have been made; and

(iii) Another version of any replacement paragraph(s), on one or more pages separate from the amendment, marked up to show all the changes relative to the previous version of the paragraph(s). The changes may be shown by brackets (for deleted matter) or underlining (for added matter), or by any equivalent marking system. A marked up version does not have to be supplied for an added paragraph or a deleted paragraph as it is sufficient to state that a particular paragraph has been added, or deleted.

(2) Amendment by replacement section . If the sections of the specification contain section headings as provided in § § 1.77(b), 1.154(b), or § 1.163(c), amendments to the specification, other than the claims, may be made by submitting:

(i) A reference to the section heading along with an instruction to delete that section of the specification and to replace such deleted section with a replacement section;

(ii) A replacement section in clean form, that is, without markings to indicate the changes that have been made; and

(iii) Another version of the replacement section, on one or more pages separate from the amendment, marked up to show all changes relative to the previous version of the section. The changes may be shown by brackets (for deleted matter) or underlining (for added matter), or by any equivalent marking system.

(3) Amendment by substitute specification. The specification, other than the claims, may also be amended by submitting:

(i) An instruction to replace the specification;

(ii) A substitute specification in compliance with § 1.125(b); and

(iii) Another version of the substitute specification, separate from the substitute specification, marked up to show all changes relative to the previous version of the specification. The changes may be shown by brackets (for deleted matter), or underlining (for added matter), or by any equivalent marking system.

Applicants need to supply a clean copy of the paragraphs or sections that need to be replaced, a marked up copy of the changes made, and instructions for replacement in the specification.

3.2 37 C.F.R. §1.821(d) states:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section,

> reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Sequences are disclosed on pages 4-8 of the specification without the required reference to the sequence identifiers (SEQ ID NOS:), and the instant specification needs to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. Applicants are required to amend the specification and claims to comply with 37 C.F.R. §1.821(d). It is acknowledged that applicants attempted to amend the specification to include the sequence identifiers, but because the amendment was done incorrectly, it was not entered.

3.3 On page 2, second paragraph, the three amino acids that are critical to trypanolytic activity are identified as amino acids 105, 107 and 110, and that a mouse TNF triple mutant, T105A-E107A-E110A, lost this activity. However, the Lucas et al. paper (1994) referred to, demonstrates that it is these amino acid residues in **human** TNF- α that are critical to this activity, while in **mouse** TNF- α it is amino acids 104, 106 and 109 that are critical to this activity. On page 7, second paragraph, and page 11, first paragraph, the mouse mutant peptide (mutTip) is identified as T104A-E106A-E109A. Also, the murine wild type Long tip peptide and mutated tip peptide, SEQ ID NOS: 6 and 7, respectively, are identified in the sequence listing as of mouse origin. The inconsistency on page 2 must be corrected.

3.4 On page 10, line 10 from the bottom, "alanin" should be spelled "alanine".

Appropriate correction is required.

Claim Objections

4. Claims 19 and 20 are objected to because of the following informalities: on the third line, the word "a" should be inserted before the word "pharmaceutical" to be grammatically correct. Also, it is suggested that a comma be inserted on the last line after "Glu^{115}". Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5.1 Claims 1 and 10 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 3 and 17, respectively of copending Application No. 10/162,553. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5.2 Claims 19-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-16 and 18-30 of copending Application No. 10/162,553. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant application, the claims are drawn to compositions comprising peptides derived from the region of human TNF-α from Ser100 to Glu116 or from the region of mouse TNF-α from Ser99 to Glu115, methods of making the compositions and methods of treatment of edema using those compositions, and the claims in 10/162,553 are drawn to compositions comprising peptides derived from the same regions and either requiring only the core sequence $TX_1EX_2X_3E$ with X being any natural or unnatural amino acid or the naturally occurring human and mouse sequences, methods of making the compositions and methods of treatment of edema using those compositions. The broader genus claims of 10/162,553 would be anticipated by the species of the instant application, and the compositions comprising the various peptides, methods of making them and methods of treatment would be obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 10, 19-26 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating edema with a circularized peptide derived from the region of human TNF-α from Ser100 to Glu116 or from the region of mouse TNF-α from Ser99 to Glu115 (17 contiguous amino acids), method of preparing such a medicament comprising such a peptide or a pharmaceutical composition comprising such a peptide for treatment of edema, does not reasonably provide enablement for a non-circularized peptide of 17 amino acids, or a circularized peptide of less than 17 amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification teaches that besides producing effects by binding to TNF receptor 1 and TNF receptor 2, TNF-α can also mediate receptor-independent activities, such as membrane-inserting and sodium channel forming capacity (page 2, second full paragraph), and that the tip domain of TNF-α (amino acids Ser100 to Glu116 of human and Ser99to Glu115 of mouse) has lectin-like affinity for specific oligosaccharides, and that both the full-length TNF-α and tip peptide of TNF-α are capable of mediating a trypanolytic activity by interfering with the lysosomal integrity of the trypanosome. The specification teaches that mutants of the tip peptide in which three critical amino acids (105, 107 and 110 of human TNF-α and 104, 106 and 109 of murine TNF-α) were replaced by alanine were completely unable to mediate this activity (page

2, first full paragraph). The instant specification teaches the construction of various peptides derived from this region of human and murine TNF-α (pages 7-8). SEQ ID NO: 1 is a 14 amino acid peptide derived from Gln102 to Tyr115 of human TNF-α, SEQ ID NO: 2 is a 14 amino acid peptide derived from Gln101 to Tyr114 of murine TNF-α, SEQ ID NO: 4 is a 17 amino acid peptide derived from Ser100 to Glu116 of human TNF-α, in which the Ser100 and Glu116 are replaced by cysteines, SEQ ID NO: 5 is a 17 amino acid peptide derived from Ser99 to Glu115 of murine TNF-α, in which the Ser99 and Glu115 are replaced by cysteines, SEQ ID NO: 6 (Long tip peptide 99-115 or Ltip) is a 19 amino acid peptide derived from Ser99 to Glu115 of murine TNF-α, in which the Ser99 and Glu115 are replaced by cysteines, the original Cys100 is replaced by Gly so that the disulfide bridge could be formed between Cys99 and Cys115, and two glycines are added at the Cys99 end. SEQ ID NO: 7 (Mutated tip peptide 99-115 or mutTip) is a 19 amino acid peptide derived from Ser99 to Glu115 of murine TNF-α, which is identical to SEQ ID NO: 6 except that the amino acids at positions 104, 106 and 109 are replaced by alanine. SEQ ID NO: 8 (Scrambled tip peptide or scramblTip) is a 19 amino acid peptide derived from Ser99 to Glu115 of murine TNF-α, which is identical to SEQ ID NO: 6 except that several internal amino acids are in different order from the wild type sequence. SEQ ID NO: 9 (Short tip peptide or Stip) is an 8 amino acid peptide derived from amino acids Thr104 to Glu109 of murine TNF-α having two cysteines added at both ends. The sequences are arranged so that equivalent amino acids are aligned as follows:

SEQ ID NO: 1 (human)	QRETPEGAEAKPWY
SEQ ID NO: 2 (murine)	PKDTPEGAELKPWY
SEQ ID NO: 4 (human)	CGQRETPEGAEAKPWYC
SEQ ID NO: 5 (murine)	CGPKDTPEGAELKPWYC
SEQ ID NO: 6 (murine Ltip)	GG-CGPKDTPEGAELKPWYC
SEQ ID NO: 7 (murine mutTip)	GG-CGPKDAPAGAALKPWYC
SEQ ID NO: 8 (murine scramblTip)	GG-CGTKPWELGPDEKPAYC
SEQ ID NO: 9 (STip)	CTPEGAEC

The instant specification discloses experiments in which primary murine cells (peritoneal macrophages, lung microvascular endothelial cells and cells lacking functional TNF receptors) were treated with either the full-length murine TNF-α or a circularized tip peptide, SEQ ID NO: 6 (Ltip), and the change in current measured. The results (Figures 1 and 2, page 10, Example 1.1) showed that ion current increase was induced by both full-length and Ltip peptide, and that it was not TNF receptor dependent. The experiment also demonstrated that the ion current increase was cell type independent. In another experiment (Figure 4B, page 11, Example 1.2), Ltip peptide, MutTip peptide (SEQ ID NO: 7) and scramlbTip peptide (SEQ ID NO: 8) were tested for ion channel activity, and only Ltip was active, confirming that residues T104, E106 and E109 were essential for this effect. The hexapeptide STip (SEQ ID NO: 9), containing the 3 critical amino acids, also failed to induce a voltage-dependent current (data not shown), suggesting that this peptide is below the minimal structure carrying the ion channel effect. Ltip was also active in cells deficient in both TNF receptors, and addition of amiloride, a sodium

channel blocker, abrogated the effect of Ltip. In another experiment (Figures 5 and 6 and page 13, Example 2), isolated rat lungs were injected with 9% NaCl solution then perfused with blood, then thirty minutes later injected with 9% NaCl solution, and the weight was then followed for 150 minutes. The weight of control lungs did not decrease with time, whereas the lungs that had been pretreated with either full-length wildtype TNF-α or tip peptide (Ltip) showed a significant decrease of weight of 25% to 50%, respectively, after 150 minutes, which corresponds to diminished presence of hydrostatic edema, and demonstrates that Ltip peptide like the full-length TNF-α can lead to edema resorption. Because the Ltip peptide does not bind to TNF receptors, treatment with the Ltip peptide would be less toxic than treatment with full-length TNF-α, which has high systemic toxicity.

These experimental results are convincing that the Ltip peptide of SEQ ID NO: 6 can be used to treat edema. Because the peptides of SEQ ID NOS: 4 and 5 are similar to that of SEQ ID NO: 6, in that they have the same core amino acid structure (or in the case of the human peptide the core human structure) and have cysteine residues at both ends that would allow circularization, one of ordinary skill in the art would expect that these two peptides would also have the same effect as the peptide of SEQ ID NO: 6, and could be used to treat edema. However, one of ordinary skill in the art would not necessarily expect that peptides containing the same 17 amino acid core region lacking cysteine residues on the ends would also be effective in treating edema. The specification states on page 8:

"To theoretically retain the original TNF conformation as much as possible, Ltip, MutTip and ScamblTip peptides were circularized."

The only experiments in which a peptide showed effective change in ion conductance or decrease in edema in lungs was the Ltip peptide of SEQ ID NO: 6, which is circularized. No experiments were performed with the equivalent peptides that were not circularized. Additionally, the only effective peptide had the 17 amino acid core. Only one experiment was done with a smaller peptide, a hexapeptide containing the 3 critical amino acids, which was not effective in ion conductance. Therefore, the specification does not provide adequate guidance as to how many amino acids of the core 17 are necessary for activity. For these reasons, only peptides containing the core 17 amino acids and that are circularized are enabled for treatment of edema.

When determining if the specification is enabling for the full scope of the claimed invention, several factors are considered. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The prior art has not taught that a small peptide derived from TNF-α would be effective in treating edema. The level of skill in the art is high, and it would not require undue experimentation to determine what minimal peptide size would be effective in ion conductance or edema resportion in lungs, or if non-circularized peptides would also be effective. However, due to the complex nature of the invention, the state of the prior art and the experimental results which show only one working embodiment, it is not predictable that a non-circularized or a smaller peptide fragment would also have the same activities as the LTip peptide. The

specification hasn't identified what the minimal peptide fragment size is that would be effective in treating edema. For these reasons, the specification is not enabled for the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 19-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 19-28 are indefinite because claims 19 and 20 are incomplete methods claims. The claims fail to achieve the goal set forth in the preamble; for example, there is no effective amount recited, nor any recitation that the treatment would result in reducing edema. The remaining claims are rejected for being dependent claims.

8.1 The art considered pertinent to the present application is Lucas et al., EP 1 264 599, December 11, 2002, which discloses TNF-derived polypeptides derived from the region of human TNF-α from Ser100 to Glu116 useful for treating edema. This is not considered prior art, since the publication date is after the priority date of the instant application, and is cited as the closest art.

8.2 Boehm et al., CA 2,005,059, June 5, 1990, is a Canadian counterpart of DE 3841 759, cited in IDS Paper No. 12. This reference does not teach or suggest what is being claimed, but is cited as being an English language equivalent.

Allowable Subject Matter

9. Methods of treatment of edema with the peptides of SEQ ID NOS: 4, 5 and 6 and pharmaceutical compositions comprising those peptides are free of the prior art and are enabled.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Eileen B. O'Hara

Patent Examiner